Claim Objections

The Examiner stated that in claim 19, line 2, the word "a" is missing between "of" and "macrovessel".

In reply, applicants have amended claim 19 accordingly.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner maintained the rejection of claims 1-10, 12-27 and 29-35 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement "to prevent accelerated development of atherosclerosis in a subject predisposed thereto", or "to inhibit progression of macrovessel disease in a subject predisposed thereto". The Examiner stated that the specification discloses an example of treatment (page 32, line 33+) of artificially induced diabetic knockout mice (that are apolipoprotein E deficient, page 31, line 9-12) with sRAGE, the treatment being started two weeks after induction of diabetes and continuing for 6 weeks, and that in these artificially induced diabetic mice, atherosclerotic plaques at the major branches of the aortic tree and at the arch of the aorta were markedly diminished in the mice treated with sRAGE (Figure 3). The Examiner stated, however, that the specification is not enabled for a method of prevention of accelerated development of atherosclerosis or inhibition of progression of a macrovessel disease. The Examiner stated that the example provided refers to a case of artificially induced diabetes in apolipoprotein E deficient mice, where the time of start of the disease is clearly known, where the evolution of the disease is monitored, where intervention is practiced at an early stage, like possibly a stage where the AGEs are not "sticking" to the cell walls, wherein a soluble form of RAGE can possibly "trap" the AGEs. The Examiner stated that atherosclerosis and macrovessel diseases are usually diseases that develop over an

extended period of time, that do not show symptoms for long periods of time, and for which the "starting point" is unknown. The Examiner stated that even if numerous risk factors for atherosclerosis have been cited in the medical and scientific literature, there is no clear parameter defining who is predisposed to develop it, at which stage of their life, under which circumstances, and how and when the polypeptide should be administered. The Examiner stated that the susceptibility to atherosclerosis and macrovessel disease varies greatly among individuals exposed to identical risk factors, and it is allegedly unpredictable which individuals are going to develop the disease and over which period of time. The Examiner stated that the specification does not provide guidance about how to determine who is predisposed to develop the diseases or at which stage of the disease the polypeptide should be administered. The Examiner alleged that it is unpredictable if the prevention will work in an established or an advanced stage of disease, in a case of naturally occurring diabetes in humans for example, or in which type of diabetes (juvenile or late onset diabetes, diabetes type I or II). The Examiner stated that it is unpredictable when to provide the treatment, for how long, and if the effect of the treatment is long term or wears off after a while and that it is even less predicable if the prevention method would work in other diseases where atherosclerosis and macrovessel disease are not associated specifically with diabetes, like different types of hyperlipidemia or hypothyroidism. The Examiner took the position that in view of the lack of guidance and working example, considering the state of the art and that it is unpredictable who is predisposed to develop the disease and when the preventive treatment should be applied, it would constitute undue experimentation to make and/or use the invention commensurate in scope with the claims.

The Examiner stated that applicants argue that the specification gives a full description of clinical signs, biochemical signs and

hereditary disorders which would indicate that a person is predisposed to accelerated atherosclerosis and that while the Examiner agrees that numerous risk factors are known (like high blood pressure, obesity) which may play a role in the development of vascular diseases, it is still unpredictable how to determine who is predisposed to develop the vascular diseases (like, for example, which person is drinking soft as opposed to hard water), and who would be prevented from accelerated development of atherosclerosis, at which stage of the disease, under which conditions, through the administration if a soluble receptor for advanced glycation product, or a derivative thereof that inhibits the interaction of AGE and RAGE. Further, the Examiner stated, the model system used (artificially induced diabetes in knockout mice) is not predictive in such patients, for reasons cited above.

Consequently, the Examiner stated that the amendments to claim 1 and 19 do not obviate the rejections because it is still unpredictable as to which population of patients, at which stage of the disease, for which specific type of disease (which macrovessel disease, for example) the method should apply, and in view of the state of the art, it would constitute undue experimentation to practice the invention commensurate in scope with the claims.

Thus, the Examiner stated, claims 1 and 19 remain rejected under 35 U.S.C. §112, first paragraph, for reasons of record in the former Office action.

The Examiner stated that claims 1 and 19 now recite a polypeptide comprising the V domain of sRAGE or a derivative thereof capable of inhibiting the interaction between AGE and RAGE. While the definition of a derivative of soluble receptor for sRAGE (page 8, line 3 through page 9, line 8) includes a soluble extracellular portion of the receptor and an antibody

specifically capable of binding to the receptor for RAGE, claims 14 and 31 remain rejected for the reasons in the Office Action of 6/24/99, page 3, because they are not enabled for a peptidomimetic or a polypeptide analog.

In reply, applicants respectfully traverse the rejection under 35 U.S.C. §112, first paragraph and maintain that the claimed invention is fully enabled by the specification.

Applicants' claimed invention is a method to prevent accelerated development of atherosclerosis in a subject predisposed thereto which comprises administering to the subject a polypeptide comprising the V-domain of sRAGE or a derivative thereof capable of inhibiting the interaction between AGE and RAGE in an amount effective to prevent accelerated development of atherosclerosis in the subject (see claim 1). Applicants believe that with regard to the Examiner's rejections under 35 U.S.C. §112, first paragraph, the Examiner may have misapprehended applicants' invention.

With respect to the Examiner's concern that atherosclerosis and macrovessel diseases are usually diseases "that develop over an extended period of time, that do not show symptoms for long periods of time and for which the starting point is unknown" (see page 3, lines 10-13 of the Office Action), applicants note that those of skill in the art do not need to know the "starting point" of the disease to practice the instant invention because applicants claim the prevention of the **progression** of accelerated atherosclerosis and not the prevention of the **initiation** of the disease. Applicants' invention is enabled because one of skill in the art would have already known, though methods commonly available to to those of skill, that the person to be treated already has the disease. Given the aforementioned information, i.e. that a person has the disease, applicants' invention could be applied to prevent the accelerated development of the disease

without undue experimentation via the teaching provided in the subject application.

Secondly, the Examiner's concern regarding "no clear parameter defining who is predisposed to develop it" (see page 3, lines 13-14 of the Office Action), is misplaced. Applicants are not claiming prevention of the disease as it applies to the predisposition of a person to develop atherosclerosis, but rather predisposition of a person to develop **accelerated** atherosclerosis. One of skill in the art, provided with information available prior to applicants' filing date, would have all the necessary tools to define which patients are predisposed to develop the disease. Once known, applicants' invention could be used to prevent the accelerated development of the disease.

Moreover, applicants have included the following references, attached herewith as Exhibits A-E, which show one of skill in the art would have known, prior to applicants' August 5, 1997 filing date, which patients would be subjects of applicants' claimed method based on specific risk factors and clearly defined detection methods associated with atherosclerosis. Specifically, applicants provide evidence which includes: a study of atherosclerosis disease progression whereby a non-invasive technique that is ideally suited for both screening and follow-up of atherosclerosis is discussed (see Exhibit A). Applicants provide evidence of risk factors identified with known mechanisms involved in the atherosclerotic process (see Exhibit B). Additionally, applicants provide evidence of a computerized assessment of atherosclerotic plaque using 3D ultrasound (see Exhibit C). Moreover, applicants provide evidence of detection and quantitation of calcific atherosclerosis (see Exhibit D). Lastly, applicants provide evidence of the detection and treatment of renovascular disease: a 40 year study (see Exhibit E).

Applicants urge that one of ordinary skill in the art would have a reasonable expectation of success in view of the disclosed risk factors and physical, biochemical, hereditary, medical and cellular characteristics known to correspond to a subject predisposed to atherosclerosis or microvessel disease. Applicants emphasize that the claimed invention is directed to "prevention of accelerated development atherosclerosis" which is a prevention of the worsening of the condition or progression of the disease at an accelerated rate, not the complete prevention of the genesis of atherosclerosis or atherogenic lesions in a completely healthy individual.

Lastly, applicants direct the Examiner's attention to *In Re Marzocchi*, 439 F.2d 220, 224, where the court stated,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain ***why*** it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Applicants maintain that the Examiner did not provide any evidentiary basis for supporting such rejections as is the Examiner's burden under the enablement requirement (see M.P.E.P. §2164.04).

As to the Examiner's concern regarding peptidomimetic or polypeptide analog, applicants traverse the rejection and submit that claims 14 and 31 are fully enabled by the subject specification combined with what would have been known to one of skill in the art at the time of applicants' effective filing date. Specifically, one would have known how to make and use a peptidomemetic of a given peptide in view of applicants' teaching in the specification at page 9, line 10 to page 11, line 34.

Therein, many embodiments of polypeptide analogs are described and early references are provided to guide the skilled person. In addition, numerous examples of modifications are provided in order to obtain a peptidomemetic (see page 11, lines 25-34). In addition to applicants' teaching, one of skill would have been cognizant of U.S. Patent 5,470,753, U.S. Patent 5,395,750 and U.S. Patent 5,331,573 which provide detailed guidance as to how to make peptidomimetics given a known peptide. Finally, applicants point out that it is not required for patentability to enable **all** embodiments of a claimed invention. Applicants, in this case, have provided an enabling disclosure for one of skill in the art to make and use the claimed invention without undue experimentation. In view of the discussion and evidence presented, applicants request reconsideration and withdrawal of this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $445.00 for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231

12/14/12

John P. White Date
Reg. No. 28,678